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* * * * * Welcome to STN International * * * * *

NEWS	1	Web Page URLs for STN Seminar Schedule - N. America
NEWS	2	"Ask CAS" for self-help around the clock
NEWS	3	JAN 17 Pre-1988 INPI data added to MARPAT
NEWS	4	FEB 21 STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results
NEWS	5	FEB 22 The IPC thesaurus added to additional patent databases on STN
NEWS	6	FEB 22 Updates in EPFULL; IPC 8 enhancements added
NEWS	7	FEB 27 New STN AnaVist pricing effective March 1, 2006
NEWS	8	MAR 03 Updates in PATDPA; addition of IPC 8 data without attributes
NEWS	9	MAR 22 EMBASE is now updated on a daily basis
NEWS	10	APR 03 New IPC 8 fields and IPC thesaurus added to PATDPAFULL
NEWS	11	APR 03 Bibliographic data updates resume; new IPC 8 fields and IPC thesaurus added in PCTFULL
NEWS	12	APR 04 STN AnaVist \$500 visualization usage credit offered
NEWS	13	APR 12 LINSPEC, learning database for INSPEC, reloaded and enhanced
NEWS	14	APR 12 Improved structure highlighting in FQHIT and QHIT display in MARPAT
NEWS	15	APR 12 Derwent World Patents Index to be reloaded and enhanced during second quarter; strategies may be affected
NEWS	16	MAY 10 CA/CAPLUS enhanced with 1900-1906 U.S. patent records
NEWS	17	MAY 11 KOREAPAT updates resume
NEWS	18	MAY 19 Derwent World Patents Index to be reloaded and enhanced
NEWS	19	MAY 30 IPC 8 Rolled-up Core codes added to CA/CAPLUS and USPATFULL/USPAT2
NEWS	20	MAY 30 The F-Term thesaurus is now available in CA/CAPLUS
NEWS	21	JUN 02 The first reclassification of IPC codes now complete in INPADOC
NEWS EXPRESS		FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005. V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT http://download.cas.org/express/v8.0-Discover/
NEWS HOURS		STN Operating Hours Plus Help Desk Availability
NEWS LOGIN		Welcome Banner and News Items
NEWS IPC8		For general information regarding STN implementation of IPC 8
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Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * STN Columbus * * * * *

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=> file reg

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	1.68	1.68

FILE 'REGISTRY' ENTERED AT 16:56:36 ON 12 JUN 2006
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STRUCTURE FILE UPDATES: 11 JUN 2006 HIGHEST RN 887399-72-6
 DICTIONARY FILE UPDATES: 11 JUN 2006 HIGHEST RN 887399-72-6

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TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when
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 *
 * The CA roles and document type information have been removed from *
 * the IDE default display format and the ED field has been added, *
 * effective March 20, 2005. A new display format, IDERL, is now *
 * available and contains the CA role and document type information. *
 *

Structure search iteration limits have been increased. See HELP SLIMITS
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REGISTRY includes numerically searchable data for experimental and
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<http://www.cas.org/ONLINE/UG/regprops.html>

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 Uploading C:\Program Files\Stnexp\Queries\spermine.str

L1 STRUCTURE UPLOADED

=> sss l1 full
 SSS IS NOT A RECOGNIZED COMMAND
 The previous command name entered was not recognized by the system.
 For a list of commands available to you in the current file, enter
 "HELP COMMANDS" at an arrow prompt (=>).

=> s sss l1 full
 FULL SEARCH INITIATED 16:56:54 FILE 'REGISTRY'
 FULL SCREEN SEARCH COMPLETED - 296340 TO ITERATE

100.0% PROCESSED 296340 ITERATIONS 7 ANSWERS
 SEARCH TIME: 00.00.03

L2 7 SEA SSS FUL L1

=> file caplus biosis embase uspatful		
COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	166.94	168.62

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FILE 'USPATFULL' ENTERED AT 16:57:07 ON 12 JUN 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

=> s 12
L3 17 L2

=> dup rem 13
PROCESSING COMPLETED FOR L3
L4 17 DUP REM L3 (0 DUPLICATES REMOVED)

=> d ibib abs hitstr 1-17

L4 ANSWER 1 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:163695 CAPLUS

DOCUMENT NUMBER: 144:384807

TITLE: Guide Molecule-driven Stereospecific Degradation of
 α -Methylpolyamines by Polyamine Oxidase

AUTHOR(S): Jaervinen, Aki; Keinaenen, Tuomo A.; Grigorenko,
Nikolay A.; Khomutov, Alex R.; Uimari, Anne;
Vepsaelaeninen, Jouko; Naervaenen, Ale; Alhonen, Leena;
Jaenne, Juhani

CORPORATE SOURCE: A. I. Virtanen Institute for Molecular Sciences and
the Department of Chemistry, University of Kuopio,
Kuopio, FI-70211, Finland

SOURCE: Journal of Biological Chemistry (2006), 281(8),
4589-4595

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular
Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

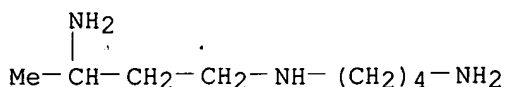
AB FAD-dependent polyamine oxidase (PAO; EC 1.5.3.11) is one of the key
enzymes in the catabolism of polyamines spermidine and spermine. The
natural substrates for the enzyme are N1-acetylspermidine,
N1-acetylspermine, and N1,N12-diacetylspermine. Here we report that PAO,
which normally metabolizes achiral substrates, oxidized (R)-isomer of
1-amino-8-acetamido-5-azanonane and N1-acetylspermidine as efficiently
while (S)-1-amino-8-acetamido-5-azanonane was a much less preferred
substrate. It has been shown that in the presence of certain aldehydes,
the substrate specificity of PAO and the kinetics of the reaction are
changed to favor spermine and spermidine as substrates. Therefore, we
examined the effect of several aldehydes on the ability of PAO to oxidize
different enantiomers of α -methylated polyamines. PAO supplemented
with benzaldehyde predominantly catalyzed the cleavage of (R)-isomer of
 α -methylspermidine, whereas in the presence of pyridoxal the
(S)- α -methylspermidine was preferred. PAO displayed the same
stereospecificity with both singly and doubly α -methylated spermine
derivs. when supplemented with the same aldehydes. Structurally related
ketones proved to be ineffective. This is the first time that the
stereospecificity of FAD-dependent oxidase has been successfully regulated
by changing the supplementary aldehyde. These findings might facilitate
the chemical regulation of stereospecificity of the enzymes.

IT 150333-68-9 878190-33-1 878190-34-2

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(guide mol.-driven stereospecific degradation of α -methylpolyamines
by polyamine oxidase)

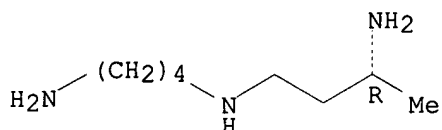
RN 150333-68-9 CAPLUS

CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



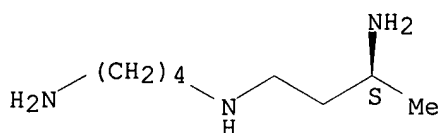
RN 878190-33-1 CAPLUS
 CN 1,3-Butanediamine, N1-(4-aminobutyl)-, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 878190-34-2 CAPLUS
 CN 1,3-Butanediamine, N1-(4-aminobutyl)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1306975 CAPLUS

DOCUMENT NUMBER: 144:212934

TITLE: α -Methyl Polyamines: Efficient Synthesis and Tolerance Studies in Vivo and in Vitro. First Evidence for Dormant Stereospecificity of Polyamine Oxidase
 AUTHOR(S): Jaervinen, Aki J.; Cerrada-Gimenez, Marc; Grigorenko, Nikolay A.; Khomutov, Alex R.; Vepsaelaeinen, Jouko J.; Sinervirta, Riitta M.; Keinaenen, Tuomo A.; Alhonen, Leena I.; Jaenne, Juhani E.

CORPORATE SOURCE: Department of Biotechnology and Molecular Medicine, A.I. Virtanen Institute for Molecular Sciences, and Department of Chemistry, University of Kuopio, Kuopio, Finland

SOURCE: Journal of Medicinal Chemistry (2006), 49(1), 399-406
 CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 144:212934

AB Efficient syntheses of metabolically stable α -methylspermidine, α -methylspermine, and bis- α,α' -methylated spermine starting from Et 3-aminobutyrate are described. The biol. tolerance for these compds. was tested in wild-type mice and transgenic mice carrying the metallothionein promoter-driven spermidine/spermine N1-acetyltransferase gene (MT-SSAT). The efficient substitution of natural polyamines by their derivs. was confirmed in vivo with the rats harboring the same MT-SSAT transgene and in vitro with the immortalized fibroblasts derived from these animals. Enantiomers of previously unknown 1-amino-8-acetamido-5-azanonane dihydrochloride (I) were synthesized starting from enantiomerically pure (R)- and (S)-alaninols. The studies with recombinant human polyamine oxidase (PAO) showed that PAO (usually splits achiral substrates) strongly favors the (R)-isomer of I that demonstrates for the first time that the enzyme has hidden potency for stereospecificity.

IT 137945-92-7P

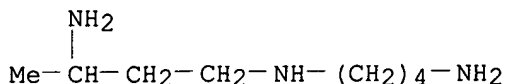
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological

activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(synthesis and tolerance studies in vivo and in vitro of spermine derivs.)

RN 137945-92-7 CAPLUS

CN 1,3-Butanediamine, N1-(4-aminobutyl)-, trihydrochloride (9CI) (CA INDEX NAME)



●3 HCl

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:149929 CAPLUS

DOCUMENT NUMBER: 142:385921

TITLE: Metabolic Stability of α -Methylated Polyamine Derivatives and Their Use as Substitutes for the Natural Polyamines

AUTHOR(S): Jaervinen, Aki; Grigorenko, Nikolay; Khomutov, Alex R.; Hyvoenen, Mervi T.; Uimari, Anne; Vepsaelaeninen, Jouko; Sinervirta, Riitta; Keinaenen, Tuomo A.; Vujcic, Slavoljub; Alhonen, Leena; Porter, Carl W.; Jaenne, Juhani

CORPORATE SOURCE: A. I. Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, FIN-70211, Finland

SOURCE: Journal of Biological Chemistry (2005), 280(8), 6595-6601

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

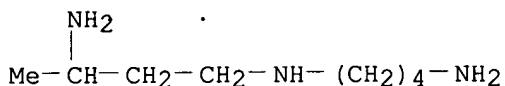
AB Metabolically stable polyamine derivs. may serve as useful surrogates for the natural polyamines in studies aimed to elucidate the functions of individual polyamines. Here we studied the metabolic stability of α -methylspermidine, α -methylspermine, and bis- α -methylspermine, which all have been reported to fulfill many of the putative physiol. functions of the natural polyamines. In vivo studies were performed with the transgenic rats overexpressing spermidine/spermine N1-acetyltransferase. α -Methylspermidine effectively accumulated in the liver and did not appear to undergo any further metabolism. On the other hand, α -methylspermine was readily converted to α -methylspermidine and spermidine; similarly, bis- α -methylspermine was converted to α -methylspermidine to some extent, both conversions being inhibited by the polyamine oxidase inhibitor N1,N2-bis(2,3-butadienyl)-1,4-butanediamine. Furthermore, we used recombinant polyamine oxidase, spermidine/spermine N1-acetyltransferase, and the recently discovered spermine oxidase in the kinetic studies. In vitro studies confirmed that methylation did not protect spermine analogs from degradation, whereas the spermidine analog was stable. Both α -methylspermidine and bis- α -methylspermine overcame the proliferative block of early liver regeneration in transgenic rats and reversed the cytostasis induced by an inhibition of ornithine decarboxylase in cultured fetal fibroblasts.

IT 150333-68-9

RL: BSU (Biological study, unclassified); BIOL (Biological study) (metabolic stability of α -methylated polyamine derivs. and their use as substitutes for natural polyamines)

RN 150333-68-9 CAPLUS

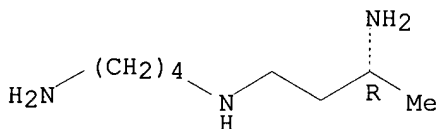
CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:688737 CAPLUS
 DOCUMENT NUMBER: 144:274446
 TITLE: Synthesis of (R)- and (S)-isomers of 1-methylspermidine
 AUTHOR(S): Grigorenko, Nikolay A.; Vepsalainen, Jouko; Jarvinen, Aki; Keinanen, Tuomo; Alhonen, Leena; Janne, Juhani; Khomutov, Alex R.
 CORPORATE SOURCE: V.A. Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, 119991, Russia
 SOURCE: Mendeleev Communications (2005), (4), 142-143
 CODEN: MENCEX; ISSN: 0959-9436
 PUBLISHER: Russian Academy of Sciences
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Previously unknown (R)- and (S)-isomers of 1,8-diamino-5-azanonane were prepared starting from (R)- and (S)-2-aminopropanols.
 IT **878133-12-1P 878133-13-2P**
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (synthesis of (R)- and (S)-isomers of 1-methylspermidine)
 RN 878133-12-1 CAPLUS
 CN 1,3-Butanediamine, N1-(4-aminobutyl)-, trihydrochloride, (3R)- (9CI) (CA INDEX NAME)

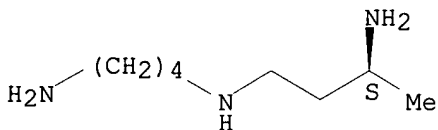
Absolute stereochemistry. Rotation (+).



● 3 HCl

RN 878133-13-2 CAPLUS
 CN 1,3-Butanediamine, N1-(4-aminobutyl)-, trihydrochloride, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● 3 HCl

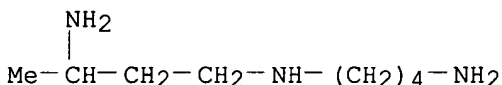
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2004:552063 CAPLUS
 DOCUMENT NUMBER: 141:82364

TITLE: Spermidine analogs for prevention and treatment of pancreatitis and induction of liver regeneration
 INVENTOR(S): Rasanen, Tiina-Liisa; Alhonen, Leena; Sinervirta, Riitta; Keinanen, Tuomo; Herzig, Karl-Heinz; Khomutov, Alex Radii; Vepsalainen, Jouko; Janne, Juhani
 PATENT ASSIGNEE(S): Tiina-Liisa Rasanen, Finland; Leena Alhonen; Riitta Sinervirta; Tuomo Keinanen; Karl-Heinz Herzig; Alex Radii Khomutov; Jouko Vepsalainen; Juhani Janne
 SOURCE: Jpn. Kokai Tokkyo Koho, 51 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2004189714	A2	20040708	JP 2003-33882	20030212
CA 2413720	AA	20040609	CA 2002-2413720	20021209
CA 2452467	AA	20040609	CA 2003-2452467	20031209
US 2004180968	A1	20040916	US 2003-731626	20031209
PRIORITY APPLN. INFO.:			US 2002-431958P	P 20021209
			CA 2002-2413720	A 20021209

OTHER SOURCE(S): MARPAT 141:82364
 AB Spermidine analogs (I; R2R1N(CR3R4)aN(R10)(CR5R6)bN(R11)[(CR7R8)cN(R12)]nR 9 wherein a, b, c = 1-6; n = 0, 1; R1-R12 = H, alkyl), including 1-methylspermidine, are claimed for prevention and treatment of pancreatitis and induction of liver regeneration.
 IT 150333-68-9
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (spermidine analogs for prevention and treatment of pancreatitis and induction of liver regeneration)
 RN 150333-68-9 CAPLUS
 CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 6 OF 17 USPATFULL on STN
 ACCESSION NUMBER: 2004:233894 USPATFULL
 TITLE: Methods for the treatment and prevention of pancreatitis and for induction of liver regeneration
 INVENTOR(S): Rasanen, Tiina-Liisa, Syvanniemi, FINLAND
 Alhonen, Leena, Vuorela, FINLAND
 Sinervirta, Riitta, Syvanniemi, FINLAND
 Keinanen, Tuomo, Kuopio, FINLAND
 Herzig, Karl-Heinz, Kuopio, FINLAND
 Khomutov, Alex Radii, Moscow, RUSSIAN FEDERATION
 Vepsalainen, Jouko, Kuopio, FINLAND
 Janne, Juhani, Vuorela, FINLAND

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004180968	A1	20040916
APPLICATION INFO.:	US 2003-731626	A1	20031209 (10)

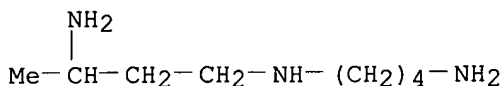
	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-431958P	20021209 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	WOODCOCK WASHBURN LLP, ONE LIBERTY PLACE, 46TH FLOOR, 1650 MARKET STREET, PHILADELPHIA, PA, 19103	
NUMBER OF CLAIMS:	30	

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Page(s)
LINE COUNT: 2039
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

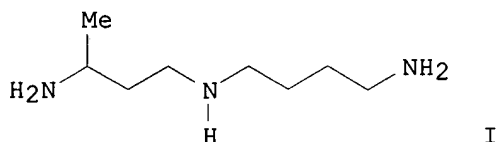
AB Novel methods for treating and preventing acute and/or chronic pancreatitis are described. Additionally, novel methods for inducing liver regeneration are described. The methods may comprise administering to a patient an effective amount of a metabolically stable analogue of spermidine and/or spermine. Preferred compounds for use in the methods may include 1-methylspermidine, 1-methylspermine and 1,12-dimethylspermine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **150333-68-9**
(spermidine analogs for prevention and treatment of pancreatitis and induction of liver regeneration)
RN 150333-68-9 USPATFULL
CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)

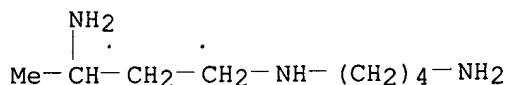


L4 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:642169 CAPLUS
DOCUMENT NUMBER: 141:395701
TITLE: A New Synthesis of α -Methylspermidine
AUTHOR(S): Grigorenko, N. A.; Vepsalainen, J.; Jarvinen, A.;
Keinanen, T. A.; Alhonen, L.; Janne, J.; Kritsyn, A.
M.; Khomutov, A. R.
CORPORATE SOURCE: Engelhardt Institute of Molecular Biology, Russian
Academy of Sciences, Moscow, 119991, Russia
SOURCE: Russian Journal of Bioorganic Chemistry (Translation
of Bioorganicheskaya Khimiya) (2004), 30(4), 396-399
CODEN: RJBCEJ; ISSN: 1068-1620
PUBLISHER: MAIK Nauka/Interperiodica Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:395701
GI



AB A five-step synthesis of α -methylspermidine (1,8-diamino-5-azanonane, I·3 HCl), the first polyamine analog preventing pathol. consequences of spermidine depletion in transgenic rats overproducing spermine/spermidine N1-acetyltransferase (no data), from Et 3-aminobutyrate was achieved in a high overall yield.

IT **137945-92-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(new synthesis of α -methylspermidine)
RN 137945-92-7 CAPLUS
CN 1,3-Butanediamine, N1-(4-aminobutyl)-, trihydrochloride (9CI) (CA INDEX NAME)



● 3 HCl

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 17 USPATFULL on STN

ACCESSION NUMBER: 2003:207355 USPATFULL
 TITLE: Novel glycosidase inhibitors and their pharmacological uses, in particular for treating diabetes
 INVENTOR(S): Aghajari, Nushin Banu Helene, Lyon, FRANCE
 Robert, Xavier Guy, Lyon, FRANCE
 Haser, Richard Michel, Lyon, FRANCE

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003143713	A1	20030731
APPLICATION INFO.:	US 2002-168703	A1	20021024 (10)
	WO 2000-FR3600		20001220

	NUMBER	DATE
PRIORITY INFORMATION:	FR 1999-16409	19991223
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	YOUNG & THOMPSON, 745 SOUTH 23RD STREET 2ND FLOOR, ARLINGTON, VA, 22202	
NUMBER OF CLAIMS:	12	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	6 Drawing Page(s)	
LINE COUNT:	959	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

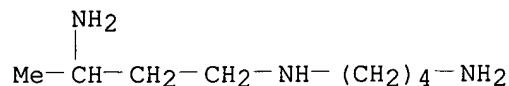
AB The invention concerns the use of a polyamine derivative or a polyamine for inhibiting the active site of glycosidase enzymes intervening in the transformation of polysaccharides into sugars, in particular into glucose, in a living organism.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 150333-68-9D, α -amylase complexes
 (polyamines and polyamine derivs. as glycosidase inhibitors and pharmacol. use, especially for treating diabetes)

RN 150333-68-9 USPATFULL

CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:489237 CAPLUS
 DOCUMENT NUMBER: 135:71297
 TITLE: Polyamines and polyamine derivatives as glycosidase inhibitors and their pharmacological uses, in particular for treating diabetes
 INVENTOR(S): Aghajari, Nushin Banu Helene; Robert, Xavier Guy; Haser, Richard Michel
 PATENT ASSIGNEE(S): Centre National de la Recherche Scientifique, Fr.
 SOURCE: PCT Int. Appl., 46 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent

LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047528	A2	20010705	WO 2000-FR3600	20001220
WO 2001047528	A3	20020620		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
FR 2802817	A1	20010629	FR 1999-16409	19991223
FR 2802817	B1	20021011		
CA 2395305	AA	20010705	CA 2000-2395305	20001220
EP 1239863	A2	20020918	EP 2000-990069	20001220
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
JP 2003518501	T2	20030610	JP 2001-548121	20001220
US 2003143713	A1	20030731	US 2002-168703	20021024
PRIORITY APPLN. INFO.:			FR 1999-16409	A 19991223
			WO 2000-FR3600	W 20001220

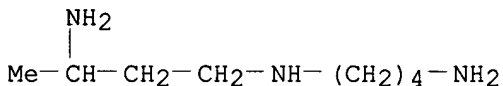
OTHER SOURCE(S): MARPAT 135:71297

AB The invention discloses the use of a polyamine or polyamine derivative for inhibiting the active site of glycosidases converting polysaccharides into sugars, in particular into glucose, in a living organism. The compds. of the invention are useful in the treatment of diabetes.

IT **150333-68-9D**, α -amylase complexes
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(polyamines and polyamine derivs. as glycosidase inhibitors and pharmacol. use, especially for treating diabetes)

RN 150333-68-9 CAPLUS

CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 10 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:252763 CAPLUS

DOCUMENT NUMBER: 135:73053

TITLE: Circular Dichroism and NMR Studies of Metabolically Stable α -Methylpolyamines: Spectral Comparison with Naturally Occurring Polyamines

AUTHOR(S): Varnado, Byron L.; Voci, Christopher J.; Meyer, Lynn M.; Coward, James K.

CORPORATE SOURCE: Departments of Medicinal Chemistry and Chemistry, The University of Michigan, Ann Arbor, MI, 48109-1055, USA

SOURCE: Bioorganic Chemistry (2000), 28(6), 395-408
CODEN: BOCMBM; ISSN: 0045-2068

PUBLISHER: Academic Press

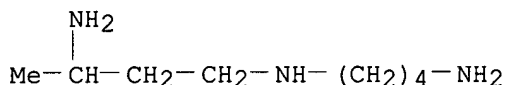
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Three synthetic polyamine analogs, α -methylspermidine, α -methylspermine, and α,α' -dimethylspermine, were compared with their naturally occurring counterparts, spermidine and spermine, by two different spectral techniques. The interaction of polyamines with oligodeoxynucleotides was measured by CD in order to monitor the polyamine-induced conversion of right-handed B-DNA to the left-handed Z-form. The methylated analogs were shown to be equally

effective as the natural polyamines in inducing the B → Z transition. The pH dependence of the chemical shift of all carbon atoms in each of the five polyamines was measured by ¹³C-NMR spectroscopy. With the exception of expected changes in chemical shift due to the presence of the α-Me substituents, the chemical shifts and pH dependence of all carbon atoms in the three α-Me polyamines were similar to the corresponding naturally occurring polyamines. The combined data indicate that α-Me polyamines have phys. properties that are very similar to their natural counterparts. The two metabolically stable polyamine analogs, α-methylspermidine and α,α'-dimethylspermine, are therefore useful surrogates for spermidine and spermine in the study of numerous polyamine-mediated effects in mammalian cell cultures and can be used in such studies without the requirement for coadministration of amine oxidase inhibitors. (c) 2000 Academic Press.

IT 150333-68-9
 RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
 (metabolically stable Me polyamine analogs have phys. properties that are very similar to their natural counterparts)
 RN 150333-68-9 CAPLUS
 CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1994:570535 CAPLUS
 DOCUMENT NUMBER: 121:170535
 TITLE: Compositions and methods for inhibiting deoxyhypusine synthase and the growth of cells
 INVENTOR(S): Jakus, Judit; Park, Myung Hee; Wolff, Edith C.; Folk, John E.
 PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA
 SOURCE: PCT Int. Appl., 50 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

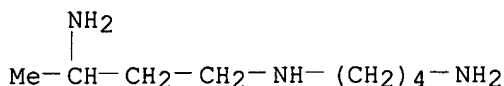
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9415596	A1	19940721	WO 1993-US12310	19931216
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5344846	A	19940906	US 1992-998231	19921230
AU 9458722	A1	19940815	AU 1994-58722	19931216
PRIORITY APPLN. INFO.:			US 1992-998231	A 19921230
			WO 1993-US12310	W 19931216

OTHER SOURCE(S): MARPAT 121:170535

AB Comps. and methods for the treatment of mammalian cells to inhibit cell growth, especially for inhibiting the proliferative cell growth associated with malignant and non-malignant disease, are provided. More particularly, a deoxyhypusine synthase inhibitor, typically, a mono- or bisguanyl diamine or polyamine, is administered to the cells. Also provided by this invention are diagnostic methods and kits for screening the cells of a patient to determine the effect of the deoxyhypusine synthase inhibitor on proliferation of the cells. Synthesis of compds. is given as is assay of enzyme inhibitory activity. Structure effects on activity is discussed.

IT 150333-68-9
 RL: PRP (Properties)
 (activity of, against deoxyhypusine synthase of rat testis)
 RN 150333-68-9 CAPLUS

CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 12 OF 17 USPATFULL on STN
ACCESSION NUMBER: 94:77732 USPATFULL
TITLE: Compositions and methods for inhibiting deoxyhypusine synthase and the growth of cells
INVENTOR(S): Jakus, Judit, Silver Spring, MD, United States
Park, Myung H., Potomac, MD, United States
Wolff, Edith C., Bethesda, MD, United States
Folk, John E., Derwood, MD, United States
PATENT ASSIGNEE(S): The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5344846		19940906
APPLICATION INFO.:	US 1992-998231		19921230 (7)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	O'Sullivan, Peter		
LEGAL REPRESENTATIVE:	Townsend and Townsend Khourie and Crew		
NUMBER OF CLAIMS:	5		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	7 Drawing Figure(s); 6 Drawing Page(s)		
LINE COUNT:	1121		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods for the treatment of mammalian cells to inhibit cell growth, especially for inhibiting the proliferative cell growth associated with malignant and non-malignant disease, are provided. More particularly, a deoxyhypusine synthase inhibitor, typically, a mono- or bisquanyl diamine or polyamine, is administered to the cells.

Also provided by this invention are diagnostic methods and kits for screening the cells of a patient to determine the effect of the deoxyhypusine synthase inhibitor on proliferation of the cells.

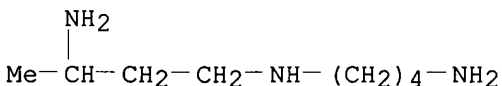
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 150333-68-9

(activity of, against deoxyhypusine synthase of rat testis)

RN 150333-68-9 USPATFULL

CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:627393 CAPLUS
DOCUMENT NUMBER: 121:227393
TITLE: The role of hypusine depletion in cytostasis induced by S-adenosyl-L-methionine decarboxylase inhibition: new evidence provided by 1-methylspermidine and 1,12-dimethylspermine
AUTHOR(S): Byers, Timothy L.; Lakanen, John R.; Coward, James K.; Pegg, Anthony E.
CORPORATE SOURCE: Department of Cell and Molecular Physiology, M.S. Hershey Medical Center, Hershey, PA, 17033, USA
SOURCE: Biochemical Journal (1994), 303(2), 363-8

DOCUMENT TYPE:

Journal

LANGUAGE:

English

AB The abilities of the natural polyamines, spermidine and spermine, and of the synthetic analogs, 1-methylspermidine and 1,12-dimethylspermine, to reverse the effects of the S-adenosyl-L-methionine decarboxylase inhibitor 5'-[[[(Z)-4-aminobut-2-enyl]methylamino]-5'-deoxyadenosine (AbeAdo) on L1210-cell growth were studied. L1210 cells were exposed to AbeAdo for 12 days to induce cytostasis and then exposed to spermidine, spermine, 1-methylspermidine or 1,12-dimethylspermine in the continued presence of AbeAdo. AbeAdo-induced cytostasis was overcome by the natural polyamines, spermidine and spermine. The cytostasis was also reversed by 1-methylspermidine. 1,12-Dimethylspermine had no effect on the AbeAdo-induced cytostasis of chronically treated cells, although it was active in permitting growth of cells treated with the ornithine decarboxylase inhibitor, α -difluoromethylornithine. The initial 12-day exposure to AbeAdo elevated intracellular putrescine levels, depleted intracellular spermidine and spermine, and resulted in the accumulation of unmodified eukaryotic translation initiation factor 5A (eIF-5A). Exposure of these cells to exogenous spermidine, which is the natural substrate for deoxyhypusine synthase, resulted in a decrease in the unmodified eIF-5A content. 1-Methylspermidine, which was found to be a substrate of deoxyhypusine synthase in vitro, also decreased the levels of unmodified eIF-5A in the AbeAdo-treated cells. Although spermine is not a substrate of deoxyhypusine synthase, spermine was converted into spermidine in the L1210 cells, and spermine addition to AbeAdo-treated cells resulted in the appearance of both intracellular spermine and spermidine and in the decrease in unmodified eIF-5A. Exogenous 1,12-dimethylspermine, which was not metabolized to spermine or to 1-methylspermidine and was not a substrate of deoxyhypusine synthase in vitro, did not decrease levels of unmodified eIF-5A. The finding that AbeAdo-induced cytostasis was only reversed by polyamines and polyamine analogs that result in the formation of hypusine or an analog in eIF-5A is consistent with the hypothesis (Byers, T. L., 1993) that AbeAdo-induced cytostasis is due to the depletion of the hypusine-containing form of eIF-5A, which is secondary to the depletion of spermidine by inhibition of S-adenosyl-L-methionine decarboxylase.

IT 150333-68-9

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(evidence provided by 1-methylspermidine and 1,12-dimethylspermine for the role of hypusine depletion in cytostasis induced by S-adenosyl-L-methionine decarboxylase inhibition)

RN 150333-68-9 CAPLUS

CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)

NH₂

$$\text{Me}-\text{CH}-\text{CH}_2-\text{CH}_2-\text{NH}-(\text{CH}_2)_4-\text{NH}_2$$

L4 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1993:576449 CAPLUS

DOCUMENT NUMBER: 119:176449

TITLE: Features of the spermidine-binding site of deoxyhypusine synthase as derived from inhibition studies. Effective inhibition by bis- and mono-guanylated diamines and polyamines

AUTHOR(S): Jakus, Judit; Wolff, Edith C.; Park, Myung Hee; Folk, J. E.

CORPORATE SOURCE: Lab. Cell. Dev. Oncol., Natl. Inst. Dent. Res., Bethesda, MD, 20892, USA

SOURCE: Journal of Biological Chemistry (1993), 268(18), 13151-9

CODEN: JBCHA3; ISSN: 0021-9258

DOCUMENT TYPE:

Journal

LANGUAGE:

English

AB Several types of basic compds. structurally related to spermidine, one of the substrates for deoxyhypusine synthase, were tested as inhibitors of this enzyme. The results indicate that inhibitory compds. associate with the enzyme at the site of spermidine binding and must possess two charged primary amino or guanidino groups, or one of each. The efficiency of inhibition is related to the maximum possible distance between the primary amino groups and is adversely affected by substitutions on the secondary amino group or in the carbon chains of polyamines. The mono-guanyl derivs. are much more effective inhibitors than the parent amines or their bis-guanylated counterparts, N1-guanyl-1,7-diaminoheptane being the most effective compound with a K_i value of about 10 nM. Based on these observations a model is proposed for the spermidine-binding site of deoxyhypusine synthase. Studies with Chinese hamster ovary cells reveal a direct correlation between prevention of hypusine formation by several guanyldiamines and their in vitro inhibition of deoxyhypusine synthase. This evidence for disruption of the initial step in the post-translational maturation of eukaryotic initiation factor 5A provides a basis for the potential control of protein biosynthesis and cell proliferation.

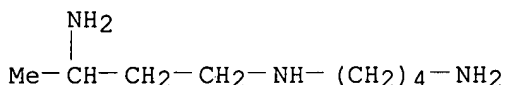
IT 150333-68-9

RL: BIOL (Biological study)

(deoxyhypusine synthase inhibition by, structure relation to)

RN 150333-68-9 CAPLUS

CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1992:105949 CAPLUS

DOCUMENT NUMBER: 116:105949

TITLE: α -Methyl polyamines: metabolically stable spermidine and spermine mimics capable of supporting growth in cells depleted of polyamines

AUTHOR(S): Lakanen, John R.; Coward, James K.; Pegg, Anthony E.
CORPORATE SOURCE: Dep. Chem., Univ. Michigan, Ann Arbor, MI, 48109-1055, USA

SOURCE: Journal of Medicinal Chemistry (1992), 35(4), 724-34
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In order to assess the tolerance of the target enzyme spermine synthase for α -substituents on the aminopropyl moiety of the substrate spermidine, 1-methylspermidine (I) was synthesized. I is a poor substrate for spermine synthase and is not a substrate for spermidine N1-acetyltransferase, suggesting that α -methylated polyamines might be metabolically stable and therefore useful tools for studying polyamine effects in intact cells. On the basis of initial cellular results with I, 1-methylspermine (II) and 1,12-dimethylspermine (III) were also synthesized. When added to cells (L1210, SV-3T3, or HT29) depleted of both putrescine and spermidine by prior treatment with α -(difluoromethyl)ornithine (IV), these α -methylated polyamines were able to restore cell growth to that observed in the absence of IV. In accord with the enzyme data noted above, metabolic studies indicated a slow conversion of I to II, but no metabolism of III in these cells. It was concluded from these results that the α -methylated polyamines are able to substitute for the natural polyamines, spermidine and spermine in critical biochem. processes which involve polyamines for continued cell growth. In accord with the hypothesis, preliminary data indicate that I and III are as effective as spermidine and spermine, resp., in promoting the conversion of B-DNA to Z-DNA.

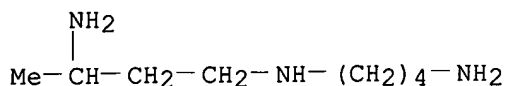
IT 137945-92-7P

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 137945-92-7 CAPLUS

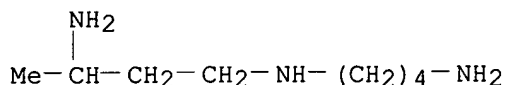
CN 1,3-Butanediamine, N1-(4-aminobutyl)-, trihydrochloride (9CI) (CA INDEX

NAME)

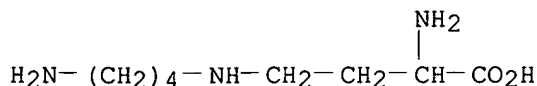


● 3 HCl

IT **150333-68-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as spermidine acetyltransferase substrate)
RN 150333-68-9 CAPLUS
CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1980:441626 CAPLUS
DOCUMENT NUMBER: 93:41626
TITLE: Coexistence of two pathways of spermidine biosynthesis
in Lathyrus sativus seedlings
AUTHOR(S): Srivenugopal, K. S.; Adiga, P. R.
CORPORATE SOURCE: Biochem. Dep., Indian Inst. Sci., Bangalore, 560012,
India
SOURCE: FEBS Letters (1980), 112(2), 260-4
CODEN: FEBLAL; ISSN: 0014-5793
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Evidence for the coexistence of both the classical S-adenosyl-L-methionine
decarboxylase pathway and a recently proposed new route (aspartic
β-semialdehyde forms a Schiff base with putrescine to be enzymically
reduced by an NADPH-dependent step to yield "carboxyspermidine", which in
turn undergoes a pyridoxal phosphate-dependent enzymic decarboxylation to
give rise to spermidine) of spermidine biosynthesis in L. sativus
seedlings is presented. The latter biosynthetic sequence is primarily
restricted to spermidine synthesis.
IT **61715-48-8**
RL: BIOL (Biological study)
(as intermediate in spermidine biosynthetic pathway in Lathyrus
sativus)
RN 61715-48-8 CAPLUS
CN Butanoic acid, 2-amino-4-[(4-aminobutyl)amino]- (9CI) (CA INDEX NAME)



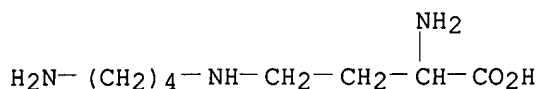
L4 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1977:52515 CAPLUS
DOCUMENT NUMBER: 86:52515
TITLE: A new pathway for the biosynthesis of spermidine
AUTHOR(S): Tait, George H.
CORPORATE SOURCE: Med. Sch., St. Mary's Hosp., London, UK
SOURCE: Biochemical Society Transactions (1976), 4(4), 610-12
CODEN: BCSTB5; ISSN: 0300-5127
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Studies of spermidine formation in *Micrococcus denitrificans* and *Rhodopseudomonas spheroides* using labeled precursors indicated the presence of an intermediate carboxyspermidine, $\text{H}_2\text{N}(\text{CH}_2)_4\text{NH}(\text{CH}_2)_2\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$ (I), formed by reduction of a Schiff's base. In the presence of pyridoxal phosphate, I was decarboxylated to spermidine.

IT 61715-48-8
 RL: BIOL (Biological study)
 (in spermidine formation, in *Micrococcus denitrificans* and *Rhodopseudomonas sphaeroides*)

RN 61715-48-8 CAPLUS

CN Butanoic acid, 2-amino-4-[(4-aminobutyl)amino]- (9CI) (CA INDEX NAME)



L7 ANSWER 3270 OF 3272 REGISTRY COPYRIGHT 2006 ACS on STN
RN 124-20-9 REGISTRY
ED Entered STN: 16 Nov 1984
CN 1,4-Butanediamine, N-(3-aminopropyl)- (8CI, 9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Spermidine (6CI)**
OTHER NAMES:
CN 1,5,10-Triazadecane
CN 1,8-Diamino-4-azaoctane
CN 4-Azaoctane-1,8-diamine
CN N-(3-Aminopropyl)-1,4-butanediamine
CN N-(3-Aminopropyl)-1,4-diaminobutane
CN N-(3-Aminopropyl)-4-aminobutylamine
CN N-(4-Aminobutyl)-1,3-diaminopropane
CN Spermidin
FS 3D CONCORD
MF C7 H19 N3
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA,
CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM,
DDFU, DETHERM*, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IPA,
MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PIRA, PROMT, RTECS*, SPECINFO,
SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

$\text{H}_2\text{N}-(\text{CH}_2)_4-\text{NH}-(\text{CH}_2)_3-\text{NH}_2$

****PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT****

9434 REFERENCES IN FILE CA (1907 TO DATE)
284 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
9446 REFERENCES IN FILE CAPLUS (1907 TO DATE)
86 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L8 ANSWER 402 OF 402 REGISTRY COPYRIGHT 2006 ACS on STN
 RN 71-44-3 REGISTRY
 ED Entered STN: 16 Nov 1984
 CN 1,4-Butanediamine, N,N'-bis(3-aminopropyl)- (8CI, 9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN **Spermine (6CI)**
 OTHER NAMES:
 CN 1,5,10,14-Tetraazatetradecane
 CN 4,9-Diazadodecane-1,12-diamine
 CN Gerontine
 CN Musculamine
 CN N,N'-Bis(3-aminopropyl)-1,4-butanediamine
 CN N,N'-Bis(3-aminopropyl)-1,4-tetramethylenediamine
 CN Neuridine
 CN NSC 268508
 CN Spermin
 FS 3D CONCORD
 DR 115-04-8
 MF C10 H26 N4
 CI COM
 LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*,
 BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS,
 CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DRUGU,
 EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS,
 NAPRALERT, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USPAT2,
 USPATFULL, VETU
 (*File contains numerically searchable property data)
 Other Sources: EINECS**, NDSL**, TSCA**
 (**Enter CHEMLIST File for up-to-date regulatory information)

$\text{H}_2\text{N}-(\text{CH}_2)_3-\text{NH}-(\text{CH}_2)_4-\text{NH}-(\text{CH}_2)_3-\text{NH}_2$

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

9218 REFERENCES IN FILE CA (1907 TO DATE)
 319 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 9230 REFERENCES IN FILE CAPLUS (1907 TO DATE)
 106 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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ACCESSION NUMBER: 81002150 EMBASE

DOCUMENT NUMBER: 1981002150

TITLE: The role of phospholipase A in acute **pancreatitis**

AUTHOR: Nevalainen T.J.

CORPORATE SOURCE: Lab. Electron Microscopy, Univ. Turku, 20520 Turku 52, Finland

SOURCE: Scandinavian Journal of Gastroenterology, (1980) Vol. 15, No. 6, pp. 641-650. .

CODEN: SJGRA4

COUNTRY: Norway

DOCUMENT TYPE: Journal

FILE SEGMENT: 048 Gastroenterology
029 Clinical Biochemistry

LANGUAGE: English

ENTRY DATE: Entered STN: 9 Dec 1991

Last Updated on STN: 9 Dec 1991

AB Phospholipase A is a hydrolytic enzyme that splits one fatty acid off the phospholipid, e.g. from lecithin to form lysolecithin. Calcium ions and bile salt are essential for the enzymatic activity. The enzyme is synthesized by the pancreatic acinar cells, liberated to the pancreatic juice, and secreted in the duodenum for digestive purposes. It is synthesized and secreted under normal circumstances in enzymatically inactive as prophospholipase A, which is activated for trypsin. Phospholipase A is inhibited by e.g. zinc, EDTA, haloketones, structural analogs of the substrate, polyphloretin phosphate, antimalarial drugs of the chloroquine type, polyamines such as **spermine**, **spermidine**, and putrescine, local anesthetics related to procaine including chlorpromazine, and antibiotics including tetracycline and chloramphenicol. The pathogenetic role of phospholipase A in acute **pancreatitis** is supported by the observations that it and lysolecithin, when injected into the pancreatic duct of experimental animals, cause histologically similar changes - namely coagulation necrosis - in the gland as seen in cases of human acute **pancreatitis**. Increased phospholipase A and lysolecithin contents are found in pancreatic tissue in acute **pancreatitis**. Phospholipase A is elevated in the serum of patients with acute **pancreatitis**. Phospholipase A injected intravenously into experimental animals causes a decrease in arterial blood pressure. The respiratory distress syndrome associated with acute **pancreatitis** can be explained by the action of phospholipase A on the pulmonary surfactant, which consists of phospholipids. The enzyme may also be involved in the development of cerebral demyelination in acute **pancreatitis** and in the formation in ischemic pancreas of a myocardial depressant factor that plays an important role in various forms of circulatory shock. Specific therapy directed to the inhibition of phospholipase A in human and experimental acute **pancreatitis** has been successful with phospholipase A inhibitors such as cytidine diphosphate choline, CaNa2-EDTA, xylocaine, procaine, and chlorpromazine. It is proposed in this review that inhibition and elimination of phospholipase A by enzyme inhibitors and immunochemical means and through detoxication methods such as hemodialysis and hemoperfusion should be investigated to find a novel and effectual treatment for acute **pancreatitis**.

ACCESSION NUMBER: 2006:211169 BIOSIS

DOCUMENT NUMBER: PREV200600212898

TITLE: Trypsin activation is followed by pancreatic polyamine depletion in severe sublethal acute **pancreatitis** model.

AUTHOR(S): Jin, Hailao; Lamsa, Teemu; Sand, Juhani; Raty, Sari; Herzig, Karl-Heinz; Alhonen, Leena; Nordback, Isto

SOURCE: Gastroenterology, (APR 2005) Vol. 128, No. 4, Suppl. 2, pp. A791.

Meeting Info.: Annual Meeting of the American-Gastroenterological-Association/Digestive-Disease-Week. Chicago, IL, USA. May 14 -19, 2005. Amer Gastroenterol Assoc.

CODEN: GASTAB. ISSN: 0016-5085.

DOCUMENT TYPE: Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 29 Mar 2006

Last Updated on STN: 29 Mar 2006

AB Background: Previous findings have demonstrated that activation of polyamine catabolism in transgenic rats (over-expressing **spermidine/spermine** N'-acetyltransferase, SSAT) results in acute pancreatic inflammation, suggesting that depletion of polyamines (**spermine** and **spermidine**) may be one step in the evolution of acute **pancreatitis**. The purpose of this study was to explore this hypothesis in another model, and to study the timing of the changes in the polyamine metabolism in relation to trypsin activation. Methods: 36 rats (300g-350g) were divided into 2 groups (**pancreatitis** group and sham group). In **pancreatitis** group 0.2 ml of 2.0% sodium taurodeoxycholate was infused into the pancreatic duct. In sham group the animals underwent laparotomy only. All animals were sacrificed and sampled under anesthesia at 3h, 24h and 48h. 6 rats served as 0 hour controls without operation. Serum amylase and pancreatic SSAT activities were measured. Pancreatic histology, water content and concentrations of **spermine**, **spermidine** and trypsin activation pepticle (TAP) were analysed, Results: In the **pancreatitis** group with hyperamylasemia, pancreatic edema, and **pancreatitis** histology SSAT was induced early, in association with trypsin, resulting in substantial decrease of both **spermine** and **spermidine** (Table). Pancreatic SSAT activity and TAP content correlated with each other (correlation coefficient 0.782, $P < 0.05$), [GRAPHICS]Conclusions: Another **pancreatitis** model (sodium taurocholate **pancreatitis**) is associated with the depletion of polyamines after induction of SSAT that occurs in association with the trypsin activation. Because polyamine depletion occurs between 3 and 24 h after induction of **pancreatitis**, it may serve as a target for therapy in **pancreatitis**.

L20 ANSWER 8 OF 225 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1978:613176 CAPLUS

DOCUMENT NUMBER: 89:213176

TITLE: Polyamine metabolism in ethionine-induced rat
pancreatitis

AUTHOR(S): Yoshikawa, Daisuke

CORPORATE SOURCE: Dep. Intern. Med., Kobe Univ. Sch. Med., Kobe, Japan

SOURCE: Kobe Ika Daigaku Kiyo (1978), 37(4), 261-9

CODEN: KIDKA9; ISSN: 0375-927X

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB Changes in concentration of putrescine, **spermidine**, and **spermine** and in activity of ornithine decarboxylase were examined in pancreas of rat in which **pancreatitis** was induced by i.p. injection of ethionine in addition to protein deprivation from food for 5 days. Ornithine decarboxylase activity decreased to about 1/10 of preinjection value of 1st day of ethionine administration. Putrescine concentration increased continuously during ethionine injection, whereas **spermidine** and **spermine** decreased slowly to about 1/2 of preinjection value. After treatment for 5 days, ethionine administration was discontinued and a normal diet was given. Ornithine decarboxylase activity increased to 39-times of preinjection value 3.5 days after the discontinuation of the treatment, followed by a rapid decrease. Putrescine concentration decreased immediately after the discontinuation, whereas **spermidine** and **spermine** increased continuously and reached preinjection levels 10 days after discontinuation.

ACCESSION NUMBER: 2002:783211 CAPLUS

DOCUMENT NUMBER: 138:331376

TITLE: A Polyamine Analogue Prevents Acute
Pancreatitis and Restores Early Liver
Regeneration in Transgenic Rats with Activated
Polyamine Catabolism

AUTHOR(S): Raesaenen, Tiina-Liisa; Alhonen, Leena; Sinervirta,
Riitta; Keinaenen, Tuomo; Herzig, Karl-Heinz; Suppola,
Suvikki; Khomutov, Alex R.; Vepsaelaeninen, Jouko;
Jaenne, Juhani

CORPORATE SOURCE: A.I. Virtanen Institute for Molecular Sciences,
University of Kuopio, Kuopio, FIN-70211, Finland

SOURCE: Journal of Biological Chemistry (2002), 277(42),
39867-39872

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular
Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We recently generated a transgenic rat model for acute
pancreatitis, which was apparently caused by a massive depletion
of pancreatic polyamines **spermidine** and **spermine** due
to inducible activation of their catabolism (Alhonen, L., Parkkinen, J.
J., Keinaenen, T., Sinervirta, R., Herzig, K. H., and Jaenne, J. (2000)
Proc. Natl. Acad. Sci. U. S. A. 97, 8290-8295). When subjected to partial
hepatectomy, these animals showed striking activation of polyamine
catabolism at 24 h postoperatively with a profound decrease in hepatic
spermidine and **spermine** pools and failure to initiate
liver regeneration. Here we show that **pancreatitis** in this
model could be totally prevented, as judged by histopathol. and plasma
 α -amylase activity, by administration of 1-methylspermidine, a
metabolically stable analog of **spermidine**. Similarly, the
analog, given prior to partial hepatectomy, restored early liver
regeneration in the transgenic rats, as indicated by a dramatic increase
in the number of proliferating cell nuclear antigen-pos. hepatocytes from
about 1% to more than 40% in response to the drug. The present results
suggest that the extremely high concentration of **spermidine** in the
pancreas, in fact the highest in the mammalian body, may have a critical role
in maintaining organ integrity. The failure to initiate liver
regeneration in the absence of sufficient hepatic polyamine pools
similarly indicates that polyamines are required for proper commencement
of the regenerative process.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

(FILE 'HOME' ENTERED AT 16:51:57 ON 12 JUN 2006)

FILE 'REGISTRY' ENTERED AT 16:56:36 ON 12 JUN 2006

L1 STRUCTURE UPLOADED
L2 7 S SSS L1 FULL

FILE 'CAPLUS, BIOSIS, EMBASE, USPATFULL' ENTERED AT 16:57:07 ON 12 JUN 2006

L3 17 S L2
L4 17 DUP REM L3 (0 DUPLICATES REMOVED)

FILE 'REGISTRY' ENTERED AT 16:58:57 ON 12 JUN 2006

L5 402 S SPERIDINE OR SPERMINE
L6 3538 S SPERMIDINE OR SPERMINE
L7 3272 S SPERMIDINE
L8 402 S SPERMINE

FILE 'CAPLUS, BIOSIS, EMBASE, USPATFULL' ENTERED AT 17:00:30 ON 12 JUN 2006

L9 45511 S SPERMINE OR SPERMIDINE
L10 46273 S L9 OR 71-44-3/RN OR 124-20-9/RN
L11 46273 S L10
L12 342976 S PANCREATITIS OR PANCREASE OR GREY TURNER SIGN OR CHOLELITHIAS
L13 1712 S L11 AND L12
L14 1684 S L11 AND (PANCREATITIS OR PANCREATIC OR GREY TURNER SIGN)
L15 1678 S L14 AND (SPERMIDINE OR SPERMIN OR SPERMINE)
L16 1358 S L14 AND (SPERMIDINE)
L17 1358 FOCUS L16 1-

=> s l11 and (pancreatitis or pancrease inflammation)

L18 236 L11 AND (PANCREATITIS OR PANCREASE INFLAMMATION)

=> dup rem l18

PROCESSING COMPLETED FOR L18

L19 225 DUP REM L18 (11 DUPLICATES REMOVED)

=> focus

PROCESSING COMPLETED FOR L19

L20 225 FOCUS L19 1-

=> s l11 and (pancreatitis)

L21 236 L11 AND (PANCREATITIS)

=> d ibib abs 1-30 120

L20 ANSWER 1 OF 225 USPATFULL on STN

ACCESSION NUMBER: 2004:233894 USPATFULL

TITLE: Methods for the treatment and prevention of
pancreatitis and for induction of liver
regeneration

INVENTOR(S): Rasanen, Tiina-Liisa, Syvanniemi, FINLAND
Alhonen, Leena, Vuorela, FINLAND
Sinervirta, Riitta, Syvanniemi, FINLAND
Keinanen, Tuomo, Kuopio, FINLAND
Herzig, Karl-Heinz, Kuopio, FINLAND
Khomutov, Alex Radii, Moscow, RUSSIAN FEDERATION
Vepsalainen, Jouko, Kuopio, FINLAND
Janne, Juhani, Vuorela, FINLAND

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004180968	A1	20040916
APPLICATION INFO.:	US 2003-731626	A1	20031209 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-431958P	20021209 (60)
DOCUMENT TYPE:	Utility	

FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WOODCOCK WASHBURN LLP, ONE LIBERTY PLACE, 46TH FLOOR,
1650 MARKET STREET, PHILADELPHIA, PA, 19103
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Page(s)
LINE COUNT: 2039

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel methods for treating and preventing acute and/or chronic **pancreatitis** are described. Additionally, novel methods for inducing liver regeneration are described. The methods may comprise administering to a patient an effective amount of a metabolically stable analogue of **spermidine** and/or **spermine**. Preferred compounds for use in the methods may include 1-methylspermidine, 1-methylspermine and 1,12-dimethylspermine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 2 OF 225 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:195392 CAPLUS

DOCUMENT NUMBER: 143:303698

TITLE: Acute **pancreatitis** induced by activation of the polyamine catabolism in gene-modified mice and rats overexpressing **spermidine/spermine** N1-acetyltransferase

AUTHOR(S): Herzig, Karl-Heinz; Janne, Juhani; Alhonen, Leena
CORPORATE SOURCE: Department of Biotechnology and Molecular Medicine, A.I. Virtanen Institute for Molecular Sciences, University of Kuopio, Finland

SOURCE: Scandinavian Journal of Gastroenterology (2005), 40(1), 120-121
CODEN: SJGRA4; ISSN: 0036-5521

PUBLISHER: Taylor & Francis

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Premature intracellular activation of digestive zymogens is the initiating factor in the course of acute **pancreatitis**. In transgenic rats overexpressing **spermidine/spermine** N1-acetyltransferase (SSAT) gene under the control of an inducible mouse metallothionein I promoter, administration of zinc resulted in acute **pancreatitis** by depletion of **spermidine** and **spermine**. A sufficient pool of higher polyamine levels seems therefore essential to maintain pancreatic integrity. The induction of **pancreatitis** by activation of SSAT could be prevented by the administration of 1-methylspermidine, a metabolically stable analog of **spermidine**.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 3 OF 225 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:525360 CAPLUS

DOCUMENT NUMBER: 133:221079

TITLE: Activation of polyamine catabolism in transgenic rats induces acute **pancreatitis**

AUTHOR(S): Alhonen, Leena; Parkkinen, Jyrki J.; Keinanen, Tuomo; Sinervirta, Riitta; Herzig, Karl-Heinz; Janne, Juhani

CORPORATE SOURCE: A. I. Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, FIN-70211, Finland

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2000), 97(15), 8290-8295
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Polyamines are required for optimal growth and function of cells. Regulation of their cellular homeostasis is therefore tightly controlled. The key regulatory enzyme for polyamine catabolism is the **spermidine/spermine** N1-acetyltransferase (SSAT). Depletion of cellular polyamines has been associated with inhibition of

growth and programmed cell death. To investigate the physiolo. function SSAT, we generated a transgenic rat line overexpressing the SSAT gene under the control of the inducible mouse metallothionein I promoter. Administration of zinc resulted in a marked induction of pancreatic SSAT, overaccumulation of putrescine, and appearance of N1-acetylspermidine with extensive depletion of **spermidine** and **spermine** in transgenic animals. The activation of pancreatic polyamine catabolism resulted in acute **pancreatitis**. In nontransgenic animals, an equal dose of zinc did not affect pancreatic polyamine pools, nor did it induce **pancreatitis**. Acetylated polyamines, products of the SSAT-catalyzed reaction, are metabolized further by the polyamine oxidase (PAO) generating hydrogen peroxide, which might cause or contribute to the pancreatic inflammatory process. Administration of specific PAO inhibitor, MDL72527 [N1,N2-bis(2,3-butadienyl)-1,4-butanediamine], however, did not affect the histol. score of the **pancreatitis**. Induction of SSAT by the polyamine analog N1,N11-diethylnorspermine reduced pancreatic polyamines levels only moderately and without signs of organ inflammation. In contrast, the combination of N1,N11-diethylnorspermine with MDL72527 dramatically activated SSAT, causing profound depletion of pancreatic polyamines and acute **pancreatitis**. These results demonstrate that acute induction of SSAT leads to pancreatic inflammation, suggesting that sufficient pools of higher polyamine levels are essential to maintain pancreatic integrity. This inflammatory process is independent of the production of hydrogen peroxide by PAO.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 4 OF 225 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:320281 CAPLUS

DOCUMENT NUMBER: 144:429469

TITLE: Genetic manipulation of polyamine catabolism in rodents

AUTHOR(S): Janne, Juhani; Alhonen, Leena; Pietila, Marko; Keinanen, Tuomo A.; Uimari, Anne; Hyvonen, Mervi T.; Pirinen, Eija; Jarvinen, Aki

CORPORATE SOURCE: Department of Biotechnology and Molecular Medicine, A.I. Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, FI-70211, Finland

SOURCE: Journal of Biochemistry (Tokyo, Japan) (2006), 139(2), 155-160

CODEN: JOBIAO; ISSN: 0021-924X

PUBLISHER: Japanese Biochemical Society

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Activation of polyamine catabolism through the overexpression of **spermidine/spermine** N1-acetyltransferase (SSAT) in transgenic rodents does not only lead to distorted tissue polyamine homeostasis, manifested as striking accumulation of putrescine, appearance N1-acetylspermidine and reduction of tissue **spermidine** and/or **spermine** pools, but likewise creates striking phenotypic changes. The latter include loss of hair, lipodystrophy and female infertility. Forced expression of SSAT modulates skin, prostate and intestinal carcinogenesis, induces acute **pancreatitis** and blocks early liver regeneration. Although many of these features are directly attributable to altered tissue polyamine pools, some of them are more likely related to the greatly accelerated flux of the polyamines caused by activated catabolism and compensatorily enhanced biosynthesis.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 5 OF 225 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:552063 CAPLUS

DOCUMENT NUMBER: 141:82364

TITLE: **Spermidine** analogs for prevention and treatment of **pancreatitis** and induction of liver regeneration

INVENTOR(S): Rasanen, Tiina-Liisa; Alhonen, Leena; Sinervirta, Riitta; Keinanen, Tuomo; Herzig, Karl-Heinz; Khomutov,

PATENT ASSIGNEE(S): Alex Radii; Vepsalainen, Jouko; Janne, Juhani
 Tiina-Liisa Rasanen, Finland; Leena Alhonen; Riitta
 Sinervirta; Tuomo Keinanen; Karl-Heinz Herzig; Alex
 Radii Khomutov; Jouko Vepsalainen; Juhani Janne
 SOURCE: Jpn. Kokai Tokkyo Koho, 51 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2004189714	A2	20040708	JP 2003-33882	20030212
CA 2413720	AA	20040609	CA 2002-2413720	20021209
CA 2452467	AA	20040609	CA 2003-2452467	20031209
US 2004180968	A1	20040916	US 2003-731626	20031209
PRIORITY APPLN. INFO.:			US 2002-431958P	P 20021209
			CA 2002-2413720	A 20021209

OTHER SOURCE(S): MARPAT 141:82364
 AB **Spermidine** analogs (I; R2R1N(CR3R4)aN(R10)(CR5R6)bN(R11)[(CR7R8)
 cN(R12)]nR9 wherein a, b, c = 1-6; n = 0, 1; R1-R12 = H, alkyl), including
 1-methylspermidine, are claimed for prevention and treatment of
pancreatitis and induction of liver regeneration.

L20 ANSWER 6 OF 225 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:106729 CAPLUS

TITLE: Activated polyamine catabolism in acute
pancreatitis: α -methylated polyamine
 analogues prevent trypsinogen activation and
pancreatitis-associated mortality

AUTHOR(S): Hyvonen, Mervi T.; Herzig, Karl-Heinz; Sinervirta,
 Riitta; Albrecht, Elke; Nordback, Isto; Sand, Juhani;
 Keinanen, Tuomo A.; Vepsalainen, Jouko; Grigorenko,
 Nikolay; Khomutov, Alex R.; Kruger, Burkhard; Janne,
 Juhani; Alhonen, Leena

CORPORATE SOURCE: Department of Biotechnology and Molecular Medicine, A.
 I. Virtanen Institute for Molecular Sciences,
 University of Kuopio, Kuopio, Finland

SOURCE: American Journal of Pathology (2005), Volume Date
 2006, 168(1), 115-122
 CODEN: AJPAA4; ISSN: 0002-9440

PUBLISHER: American Society for Investigative Pathology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Polyamines are essential for normal cellular growth and function.
 Activation of polyamine catabolism in transgenic rats overexpressing
spermidine/spermine N1-acetyltransferase, the key enzyme
 in polyamine catabolism, results in severe acute **pancreatitis**.
 Here, we investigated the role of polyamine catabolism in
pancreatitis and studied the effect of polyamine analogs on the
 outcome of the disease. Polyamine depletion was associated with arginine-
 and caerulein-induced **pancreatitis** as well as with human acute
 necrotizing and chronic secondary **pancreatitis**. Substitution of
 depleted polyamine pools with methylspermidine partially prevented
 arginine-induced necrotizing **pancreatitis** whereas
 caerulein-induced edematous **pancreatitis** remained unaffected.
 Transgenic rats receiving methylated polyamine analogs after the induction
 of **pancreatitis** showed less pancreatic damage than the untreated
 rats. Most importantly, polyamine analogs dramatically rescued the
 animals from **pancreatitis**-associated mortality. Induction of
spermidine/spermine N1-acetyltransferase in acinar cells
 isolated from transgenic rats resulted in increased trypsinogen
 activation. Pretreatment of acini with bismethylspermine prevented
 trypsinogen activation, indicating that premature proteolytic activation
 is one of the effects triggered by polyamine depletion. Our data suggest
 that activation of polyamine catabolism is a general pathway in the
 pathogenesis of acute **pancreatitis** and that exptl. disease can
 be ameliorated with stable polyamine analogs.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 7 OF 225 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:783211 CAPLUS

DOCUMENT NUMBER: 138:331376

TITLE: A Polyamine Analogue Prevents Acute
Pancreatitis and Restores Early Liver
Regeneration in Transgenic Rats with Activated
Polyamine Catabolism

AUTHOR(S): Raesaenen, Tiina-Liisa; Alhonen, Leena; Sinervirta,
Riitta; Keinaenen, Tuomo; Herzig, Karl-Heinz; Suppola,
Suvikki; Khomutov, Alex R.; Vepsaelaeninen, Jouko;
Jaenne, Juhani

CORPORATE SOURCE: A.I. Virtanen Institute for Molecular Sciences,
University of Kuopio, Kuopio, FIN-70211, Finland

SOURCE: Journal of Biological Chemistry (2002), 277(42),
39867-39872

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular
Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

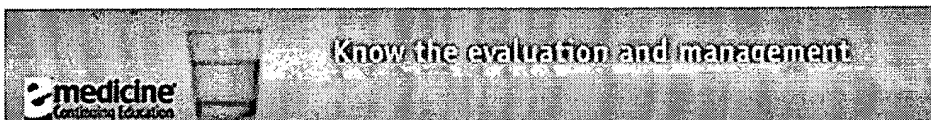
AB We recently generated a transgenic rat model for acute
pancreatitis, which was apparently caused by a massive depletion
of pancreatic polyamines **spermidine** and **spermine** due
to inducible activation of their catabolism (Alhonen, L., Parkkinen, J.
J., Keinaenen, T., Sinervirta, R., Herzig, K. H., and Jaenne, J. (2000)
Proc. Natl. Acad. Sci. U. S. A. 97, 8290-8295). When subjected to partial
hepatectomy, these animals showed striking activation of polyamine
catabolism at 24 h postoperatively with a profound decrease in hepatic
spermidine and **spermine** pools and failure to initiate
liver regeneration. Here we show that **pancreatitis** in this
model could be totally prevented, as judged by histopathol. and plasma
 α -amylase activity, by administration of 1-methylspermidine, a
metabolically stable analog of **spermidine**. Similarly, the
analog, given prior to partial hepatectomy, restored early liver
regeneration in the transgenic rats, as indicated by a dramatic increase
in the number of proliferating cell nuclear antigen-pos. hepatocytes from
about 1% to more than 40% in response to the drug. The present results
suggest that the extremely high concentration of **spermidine** in the
pancreas, in fact the highest in the mammalian body, may have a critical role
in maintaining organ integrity. The failure to initiate liver
regeneration in the absence of sufficient hepatic polyamine pools
similarly indicates that polyamines are required for proper commencement
of the regenerative process.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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June 12, 2006

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Pancreatitis

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AUTHOR INFORMATION

Section 1 of 9

[Author Information](#) [Introduction](#) [Clinical Differentials](#) [Workup](#) [Treatment](#) [Medication](#) [Follow-up](#) [Bibliography](#)

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Coauthor(s): **Samer S Deebea, MD**, Fellow, Department of Surgery, St Mary's Hospital, Imperial College, London

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Disclosure

INTRODUCTION

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Background: **Pancreatitis** is an inflammatory process in which pancreatic enzymes autodigest the gland.

The gland can sometimes heal without any impairment of function or any morphologic changes. This process known as acute **pancreatitis**. It can recur intermittently, contributing to the functional and morphologic loss of the gland. Recurrent attacks are referred to as chronic **pancreatitis**. Both forms of **pancreatitis** are present in the clinical spectrum with acute clinical findings.

Pathophysiology: Because the pancreas is located in the retroperitoneal space with no capsule, inflammation spreads easily. In acute **pancreatitis**, parenchymal edema and peripancreatic fat necrosis occur first. This process is known as acute edematous **pancreatitis**.

When necrosis involves the parenchyma, accompanied by hemorrhage and dysfunction of the gland, the inflammation evolves into hemorrhagic or necrotizing **pancreatitis**.

Pseudocysts and pancreatic abscesses can result from necrotizing **pancreatitis** because of enzymes being walled off by granulation tissue (ie, pseudocyst formation) or bacterial seeding of pancreatic or peripancreatic tissue (ie, pancreatic abscess formation). An ultrasound or, preferably, a CT scan can be used to detect both.

The inflammatory process can cause systemic effects because of the presence of cytokines, such as bradykinin and phospholipase A. These cytokines may cause vasodilation, increase in vascular permeability, pain, and leukocyte accumulation in the vessel walls. Fat necrosis may cause hypocalcemia. Pancreatic B cell injury results in hyperglycemia.

Frequency:

- **In the US:** Annual incidence of acute **pancreatitis** is 19.5 per 100,000 population and chronic **pancreatitis** is 8.3 per 100,000 population per year.

Mortality/Morbidity:

- Although acute **pancreatitis** should be noted, chronic **pancreatitis** has a more severe presentation as episodes recur.
- Acute respiratory distress syndrome (ARDS), acute renal failure, cardiac depression, hemorrhage, and hypotensive shock all may be systemic manifestations of acute **pancreatitis** in its most severe form.

Race: Annual incidence of acute **pancreatitis** in Native American persons is 4 per 100,000 population, in white persons is 5.7 per 100,000 population, and in black persons is 20.7 per 100,000 population.

Sex: No predilection exists.

Age: The risk for African American persons aged 35-64 years is 10 times higher than for any other group. African American persons are at higher risk than white persons in that same age group.

CLINICAL

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History:

- The main presentation of acute **pancreatitis** is epigastric pain or right upper quadrant pain radiating to back
- Nausea and/or vomiting
- Fever
- Query the patient about recent surgeries and invasive procedures (ie, endoscopic retrograde cholangiopancreatography) or family history of hypertriglyceridemia.
- Patients frequently have a history of previous biliary colic and binge alcohol consumption, the major cause of acute **pancreatitis**.

Physical:

- Tachycardia
- Tachypnea
- Hypotension
- Fever
- Abdominal tenderness, distension, guarding, and rigidity
- Mild jaundice
- Diminished or absent bowel sounds
- Because of contiguous spread of inflammation (effusion) from the pancreas, lung auscultation may reveal basilar rales, especially in the left lung.
- Occasionally, in the extremities, muscular spasm may be noted secondary to hypocalcemia.
- Severe cases may have a Grey Turner sign (ie, bluish discoloration of the flanks) and Cullen sign (ie, discoloration of the periumbilical area) caused by the retroperitoneal leak of blood from the pancreas in hemorrhagic **pancreatitis**.

Causes:

- The major causes are long-standing alcohol consumption and biliary stone disease.
 - In developed countries, the most common cause of acute **pancreatitis** is alcohol abuse.
 - On the cellular level, ethanol leads to intracellular accumulation of digestive enzymes and their premature activation and release.

- On the ductal level, ethanol increases the permeability of ductules, which allow enzymes to enter the parenchyma, resulting in pancreatic damage.
- Ethanol increases the protein content of the pancreatic juice and decreases bicarbonate and trypsin inhibitor concentrations. This leads to the formation of protein plugs that block the pancreatic outflow and obstruction.
- Another major cause of acute **pancreatitis** is biliary stone disease (eg, cholelithiasis, choledocholithiasis). A biliary stone may lodge in the pancreatic duct or ampulla of Vater and obstruct the pancreatic duct, leading to extravasation of enzymes into the parenchyma.
- **Minor causes of acute pancreatitis**
 - Medications, including azathioprine, corticosteroids, sulfonamides, thiazides, furosemides, NSAIDs, mercaptopurine, methyldopa, and tetracyclines
 - Endoscopic retrograde cholangiopancreatography (ERCP)
 - Hypertriglyceridemia (When the triglyceride (TG) level exceeds 1000 mg/U, an episode of **pancreatitis** is more likely.)
 - Peptic ulcer disease
 - Abdominal or cardiopulmonary bypass surgery, which may insult the gland by ischemia
 - Trauma to the abdomen or back, resulting in sudden compression of the gland against the spine posteriorly
 - Carcinoma of the pancreas, which may lead to pancreatic outflow obstruction
 - Viral infections, including mumps, Coxsackievirus, cytomegalovirus (CMV), hepatitis virus, Epstein-Barr virus (EBV), and rubella
 - Bacterial infections, such as mycoplasma
 - Intestinal parasites, such as ascaris, which can block the pancreatic outflow
 - Pancreas divisum
 - Scorpion and snake bites
- Vascular factors, such as ischemia or vasculitis

DIFFERENTIALS

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[Aneurysm, Abdominal](#)
[Cholangitis](#)
[Cholecystitis and Biliary Colic](#)
[Cholelithiasis](#)
[Gastroenteritis](#)

Hepatitis

Mesenteric Ischemia

Obstruction, Large Bowel

Obstruction, Small Bowel

Other Problems to be Considered:

Perforated viscus

Acute peritonitis

Choledocholithiasis

Macroamylasemia

Macrolipasemia

Intestinal obstruction

Pancreatic cancer

Malabsorption syndromes/processes

WORKUP

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Lab Studies:

- A complete blood count (CBC) demonstrates leukocytosis (WBC >12000) with the differential being shifted to the left.
- If blood transfusion is necessary, as in cases of hemorrhagic **pancreatitis**, obtain type and crossmatch.
- Measure blood glucose level because it may be elevated from B cell injury in the pancreas.
- Obtain measurements for BUN, creatine (Cr), and electrolytes (Na, K, Cl, CO₂, P, Mg); a great disturbance in electrolyte balance is usually found, secondary to third spacing of fluids.
- Measure amylase levels, preferably the Amylase P, which is more specific to pancreatic pathology. Levels greater than normal strongly suggest the diagnosis of acute **pancreatitis**.
- Lipase levels also are elevated and remain high for 12 days. In patients with chronic **pancreatitis** (usually alcohol abuse), lipase may be elevated in the presence of a normal serum amylase level.
- Perform liver function tests (eg, alkaline phosphatase, serum glutamic-pyruvic transaminase [SGPT], serum glutamic oxaloacetic transaminase [SGOT], G-GT) and bilirubin, particularly with biliary origin **pancreatitis**.

Imaging Studies:

- Perform a plain KUB (Kidneys, ureters, bladder) with the patient in the upright position to exclude visceral free air (under the diaphragm). In cases with a recurrent episode of chronic **pancreatitis**, peripancreatic calcifications may be seen.
- Ultrasound can be used as a screening test. If overlying gas shadows secondary to bowel distention are present, it is not specific.
- CT scan is the most reliable imaging modality in the diagnosis of acute **pancreatitis**. The criteria for diagnosis are:

Balthazar and colleagues into 5 grades, as follows:

- Grade A - Normal pancreas
 - Grade B - Focal or diffuse gland enlargement
 - Grade C - Intrinsic gland abnormality recognized by haziness on the scan
 - Grade D - Single ill-defined collection or phlegmon
 - Grade E - Two or more ill-defined collections or the presence of gas in or nearby the pancreas
- The use of contrast material intravenously is yet to be proved detrimental on the microcirculation of the necrotizing **pancreatitis**.

Other Tests:

- Para-aminobenzoic acid test (ie, bentiromide [Chymex] test) for chronic **pancreatitis**

TREATMENT

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Emergency Department Care: Most of the cases presenting to the ED are treated conservatively, and appropriate treatment.

- Fluid resuscitation
 - Monitor accurate intake/output and electrolyte balance of the patient.
 - Crystalloids are used, but other infusions, such as packed red blood cells (PRBCs), are occasionally used in the case of hemorrhagic **pancreatitis**.
 - Central lines and Swan-Ganz catheters are used in patients with severe fluid loss and very low blood pressure.
- Patients should have nothing by mouth, and a nasogastric tube should be inserted to assure an empty stomach at rest.
- Begin parenteral nutrition if the prognosis is poor and if the patient is going to be kept in the hospital for more than 7 days.
- Analgesics are used to relieve pain. Meperidine is preferred over morphine because of the greater spasm of the sphincter of Oddi.
- Antibiotics are used in severe cases associated with septic shock or when the CT scan indicates that infection has evolved.
- Other conditions, such as biliary **pancreatitis** associated with cholangitis, also need antibiotic coverage. These are the ones secreted by the biliary system, such as ampicillin and third generation cephalosporins.
- Continuous oxygen saturation should be monitored by pulse oximetry and acidosis should be corrected. If pending respiratory failure develops, intubation should be performed.

- Perform CT-guided aspiration of necrotic areas, if necessary.
- An ERCP may be indicated for common duct stone removal.

Consultations: Consult a general surgeon in the following cases:

- For phlegmon of the pancreas, surgery can achieve drainage of any abscess or scooping of necrotic p followed by postoperative lavage of the pancreatic bed.
- In patients with hemorrhagic **pancreatitis**, surgery is indicated to achieve hemostasis, particularly bec eroded in acute **pancreatitis**.
- Patients who fail to improve despite optimal medical treatment or patients who push the Ranson score operating room. Surgery in these cases may lead to a better outcome or confirm a different diagnosis.
- In biliary **pancreatitis**, a sphincterotomy (ie, surgical emptying of the common bile duct) can relieve th cholecystectomy may be performed to clear the system from any source of biliary stones.



Targeting Abdominal Obesity to Reduce Cardiovascular Risk in Patients With Type 2 Diabetes

This activity is composed of the following audio/slide presentations:

- Welcome and Program Introduction (Alan D. Cherrington, PhD)
- Why Abdominal Obesity Increases Metabolic and Cardiovascular Risk in Type 2 Diabetes: The Preclinical Evidence (Richard N. Bergman, PhD)
- The Endocannabinoid System: The Mechanisms Behind Metabolic Homeostasis and Imbalance (Stephen C. Woods, PhD)
- Endocannabinoid Blockade for Improving Glycemic Control and Lipids in Patients With Type 2 Diabetes (Priscilla Hollander, MD, PhD)
- Panel Discussion (Moderator Louis J. Aronne, MD, FACP, with panelists Richard Bergman, PhD; Alan D. Cherrington, PhD; Robert R. Henry, MD; Priscilla Hollander, MD, PhD; and Stephen C. Woods, PhD)

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MEDICATION

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The goal of pharmacotherapy is to relieve pain and minimize complications.

Drug Category: Antibiotics -- Used to cover the microorganisms that may grow in biliary **pancreatitis** and **pancreatitis**. The empiric antibiotic regimen usually is based on the premise that enteric anaerobic and aer microorganisms are often the cause of pancreatic infections. Once culture sensitivities are made, adjustmer can be done.

Drug Name	Ceftriaxone (Rocephin) -- Third-generation cephalosporin with broad negative activity; lower efficacy against gram-positive organisms; highly resistant organisms. Arrests bacterial growth by binding to one or more proteins.
Adult Dose	1-2 g IM/IV once or divided bid
Pediatric Dose	50-75 mg/kg/d IM/IV divided q12h
Contraindications	Documented hypersensitivity
Interactions	Probenecid may increase levels; coadministration with ethacrynic acid and aminoglycosides may increase nephrotoxicity
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Adjust dose in renal impairment; caution in breastfeeding women and newborns
Drug Name	Ampicillin (Marcillin, Omnipen) -- Bactericidal activity against susceptible gram-negative organisms. Alternative to amoxicillin when unable to take medication orally.
Adult Dose	250-500 IM/IV mg q6h
Pediatric Dose	25-50 mg/kg/d IM/IV divided q6-8h
Contraindications	Documented hypersensitivity; viral mononucleosis
Interactions	Probenecid and disulfiram elevate levels; allopurinol decreases effects on ampicillin rash; may decrease effects of oral contraceptive
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Adjust dose in renal failure; evaluate rash and differentiate from hyp

Drug Category: Analgesics -- Pain control is essential to quality patient care. It ensures patient comfort, and has sedating properties, which are beneficial for patients who have sustained trauma or have painful lesions.

Drug Name	Meperidine (Demerol) -- Analgesic with multiple actions similar to those of morphine but produce less constipation, smooth muscle spasm, and depression of respiration at similar analgesic doses of morphine.
Adult Dose	15-35 mg/h IV; 50-150 mg IM q3-4h
Pediatric Dose	1.1-1.8 mg/kg IM q3-4h
Contraindications	Documented hypersensitivity; MAOIs; upper airway obstruction or severe respiratory depression; during labor when delivery of premature infant is anticipated
Interactions	Monitor for increased respiratory and CNS depression with coadministration of sedatives; hydantoins may decrease effects; avoid with protease inhibitors
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in head injuries because may increase respiratory depression (use only if absolutely necessary); caution when using postoperative analgesics in patients with pulmonary disease (suppresses cough reflex; substantially increase risk of pneumonia); may aggravate or cause seizures because of tolerance, even if no prior history of seizures; monitor closely for morphine-induced seizure activity if seizure disorders

FOLLOW-UP

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Further Inpatient Care:

- Transfer patients with Ranson scores of 0-2 to a hospital floor.

- Transfer patients with Ranson scores 3-5 to an intensive care unit.
- Transfer patients with Ranson scores higher than 5 to an intensive care unit with emergency surgery and
- Two other systems, the Acute Physiology and Chronic Health Evaluation (APACHE) and the Multiple Organ Dysfunction Score (MODS) have been used recently, but these are used more in an ICU setting.

Further Outpatient Care:

- The patient should be followed routinely with physical examination and amylase and lipase assays.

Complications:

- Infected pancreatic necrosis may result from seeding of bacteria into the inflammation.
- An acute pseudocyst is an effusion of pancreatic juice that is walled off by granulation tissue after an episode of pancreatitis.
- Hemorrhage into the GI tract retroperitoneum or the peritoneal cavity is possible because of erosion of blood vessels.
- Intestinal obstruction or necrosis may occur.
- Common bile duct obstruction may be caused by a pancreatic abscess, pseudocyst, or biliary stone that compresses the duct.
- An internal pancreatic fistula from pancreatic duct disruption or a leaking pancreatic pseudocyst may cause abdominal pain.

Prognosis:

- Ranson developed a series of different criteria for the severity of acute **pancreatitis**.
 - Present on admission
 - Older than 55 years
 - WBC higher than 16,000 per mcL
 - Blood glucose higher than 200 mg/dL
 - Serum lactate dehydrogenase (LDH) more than 350 IU/L
 - SGOT (ie, aspartate aminotransferase [AST]) greater than 250 IU/L
 - Developing during the first 48 hours
 - Hematocrit fall more than 10%
 - BUN increase more than 8 mg/dL
 - Serum calcium less than 8 mg/dL
 - Arterial oxygen saturation less than 60 mm Hg

- Base deficit higher than 4 mEq/L
- Estimated fluid sequestration higher than 600 mL
- A Ranson score of 0-2 has a minimal mortality rate.
- A Ranson score of 3-5 has a 10%-20% mortality rate.
- A Ranson score higher than 5 has a mortality rate of more than 50% and is associated with more syst

Patient Education:

- Educate patients about the disease and advise them to avoid alcohol in binge amounts and to disconti fatty meals and abdominal trauma.
- For excellent patient education resources, visit eMedicine's [Liver, Gallbladder, and Pancreas Center](#). / education article, **Pancreatitis**.

BIBLIOGRAPHY

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